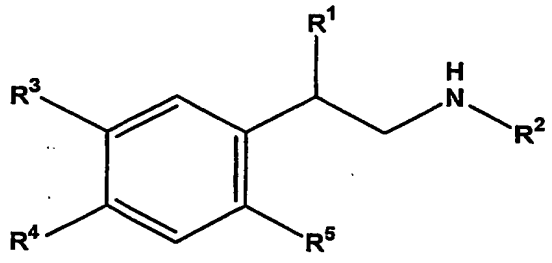
CLAIMS

1. A multifunctional β-agonist compound being ROS scavenger and NO donor of Formula 1:



or its salt, wherein R^1 is selected from the group consisting of —OH, —ONO, —ONO_2, —SNO, and —NONOate;

R^2 is ROS scavenger group or a NO donor group connected to the —NH group via a linker made of C_5-C_8 cyclic alkyl, or straight or branched C_1-C_{15} alkyl in which one carbon atom is optionally replaced by oxygen or nitrogen, wherein said ROS scavenger group is selected from a nitroxide free radical, alkenyl, sulfhydryl or dithiol moiety in oxidized or reduced form, and aryl, and wherein said NO donor group is selected from —ONO, —ONO_2, —SNO, and —NONOate or R^2 is C_5-C_8 cyclic alkyl, or straight or branched C_1-C_{15} alkyl;

R^3 and R^4 are independently selected from the group consisting of —OH, —CH_2OH, —NH_2, —NHCHO, or R^3 and R^4 together form a substituted 5 to 7-membered saturated heterocycle having 1 or 2 heteroatoms independently selected from nitrogen, and oxygen, and sulfur, or R^3 and R^4 together form amino or hydroxy protecting groups selected from N-formyl, acetal, and ketal;

R^5 is selected from the group consisting of —H, —OH, —CH_2OH, —NH_2, —NHCHO, straight or branched chain C_1-C_{15} alkyl, and straight or branched chain C_1-C_{15} alkoxy;

whereas said RO scavenger moieties are optionally substituted with one or more C_1-C_{15} alkyl groups, C_1-C_{15} alkoxy groups, phenyl, —NH_2, —NHCHO, —OH, —CH_2OH, and groups capable of donating NO in a charged or neutral form; and

whereas any of said alkyl groups is optionally substituted with one or more functional groups selected from hydroxyl, bromo, fluoro, chloro, iodo, mercapto or thio, cyano, alkylthio, aryl, carboxyl, carbalkoyl, alkenyl, nitro, amino, alkoxyl, amido;

wherein at least one of R^1, R^2, R^3 and R^4 comprises at least one ROS scavenger selected from the group of moieties consisting of a nitroxide free radical, alkenyl, sulfhydryl or dithiol in oxidized or reduced form, and aryl; and

wherein at least one of R^1, R^2, R^3 and R^4 comprises at least one NO donor selected from —ONO, —ONO_2, and —SNO.

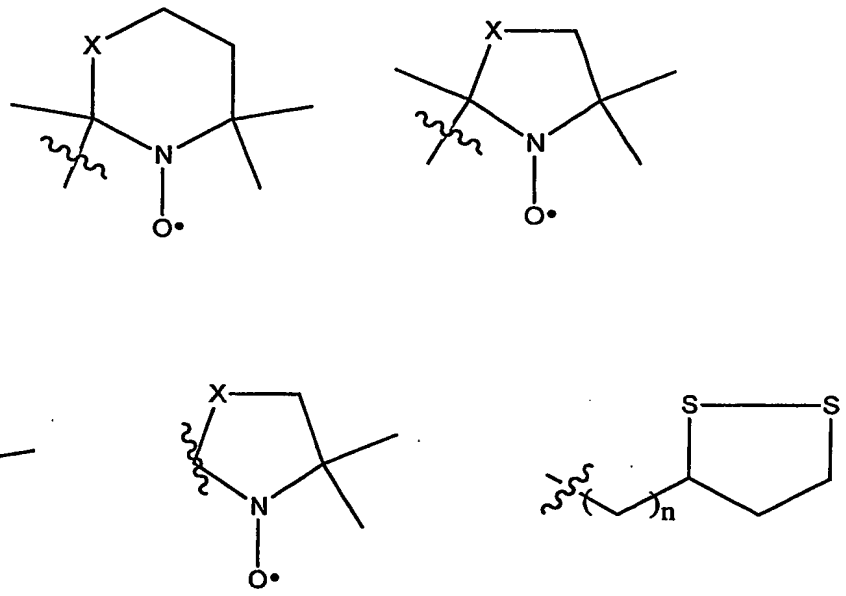
2. A β-agonist compound according to claim 1, wherein said saturated heterocycle is selected from the group consisting of pyrrolidine, oxazolidine, thiazolidine, tetrahydro 1,3-oxazine, 1,3-dioxane, piperidine, 3-thiapiperidine, and 1,3-thiazine.

3. A β-agonist compound according to claim 1, wherein said saturated heterocycle comprises a substituted nitroxide free radical.

4. A β-agonist compound according to claim 1, wherein the nitroxide free radical is a heterocyclyl moiety having the nitrogen atom within a 5-, 6- or 7-membered ring which optionally contains another heteroatom selected from oxygen and sulfur at position beta to the nitrogen, and which is substituted with methyl or ethyl at positions alpha to the nitrogen.

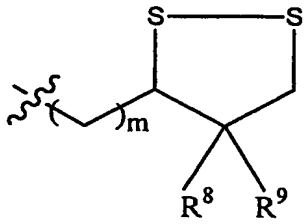
5. The β-agonist compound of claim 4, wherein said heterocyclyl moiety is linked to the β-agonist moiety via sharing of 1 to 2 atoms, or via a linker.

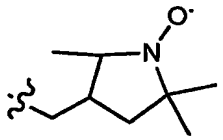
6. A β-agonist compound according to any one of claims 1 to 5, wherein said ROS scavenger is selected from the group consisting of the following moieties:



wherein X is selected from carbon, oxygen, and sulfur, and n is an integer from 1 to 15.

7. A β-agonist compound according to claim 1, wherein R^2 is selected from the following structures:


S
S
m
R8
R9


O
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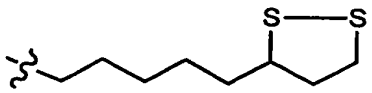
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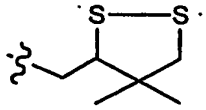
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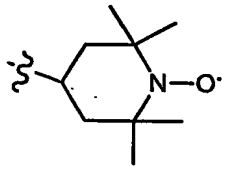
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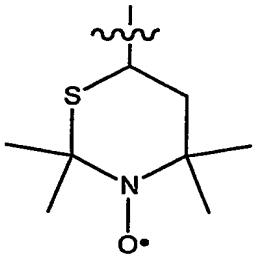
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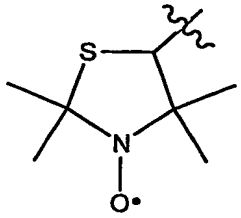
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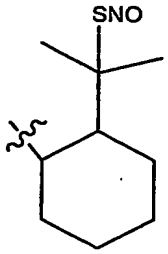
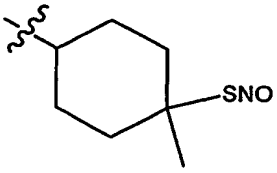

SNO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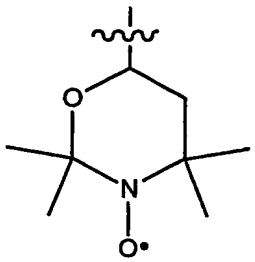
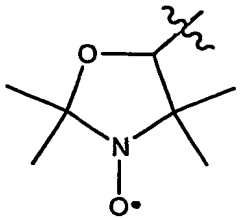
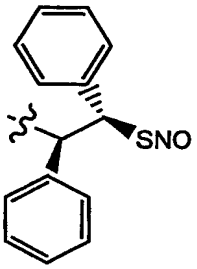
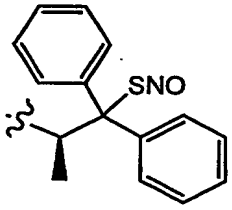


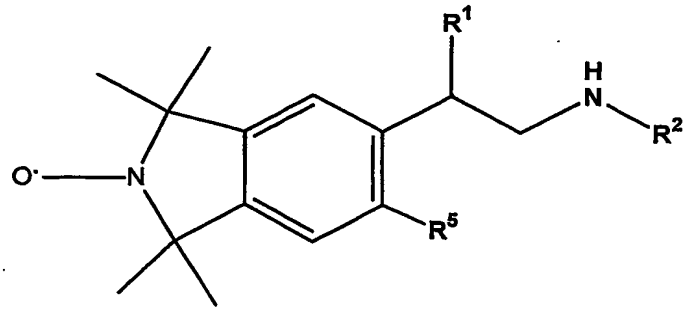






wherein m is 1-6 and R^8 and R^9 are independently C_1-C_3 alkyl or —H.

8. A β-agonist compound having the formula:

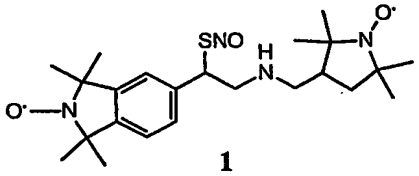


or its salt; wherein R^1 is selected from the group consisting of —OH, —ONO, —ONO_2, and —SNO;

R^5 is hydrogen;

and R^2 is a moiety selected from a nitroxide free radical having the nitrogen atom within a 5-, 6- or 7-membered saturated ring and which is substituted by up to four methyl groups at positions alpha to the nitrogen, sulfhydryl or dithiol moiety in oxidized or reduced form, —ONO, —ONO_2, and —SNO, wherein said moiety is connected to the —NH group directly or via a linker made of C_1-C_6 alkyl, and which linker is optionally substituted by one or more phenyl groups.

9. A multifunctional β-agonist compound according to claim 1 having one of the following structures:



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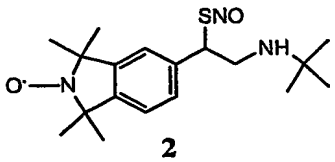

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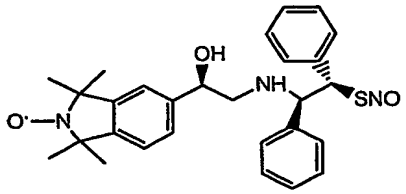

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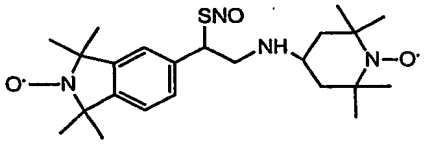

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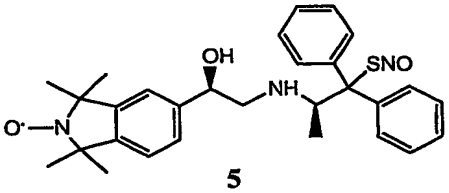

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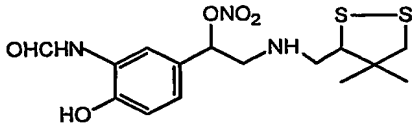

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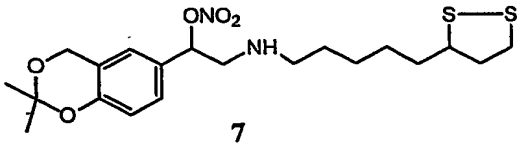

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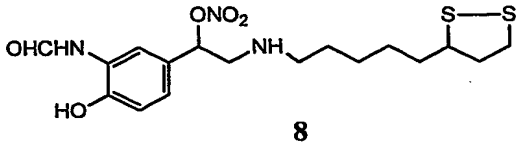

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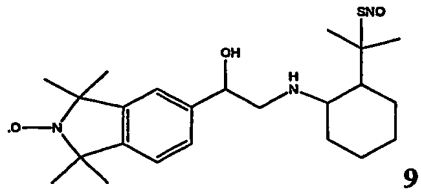

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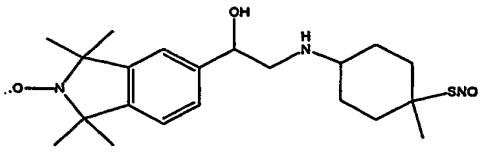

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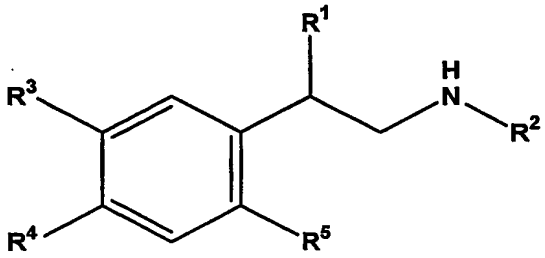
10. A process of preparing a compound of Formula 1:



or its salt, wherein R^1 is selected from the group consisting of —OH, —ONO, —ONO_2, and —SNO;

R^2 is ROS scavenger group or a NO donor group connected to the —NH group via a linker made of C_5-C_8 cyclic alkyl, or straight or branched C_1-C_{15} alkyl, wherein said ROS scavenger group is selected from a nitroxide free radical, alkenyl, sulfhydryl or dithiol moiety in oxidized or reduced form, and aryl, and wherein said NO donor group is selected from —ONO, —ONO_2, and —SNO or R^2 is C_5-C_8 cyclic alkyl, or straight or branched C_1-C_{15} alkyl;

R^3 and R^4 are independently selected from the group consisting of —OH, —CH_2OH, —NH_2, —NHCHO, or R^3 and R^4 together form a nitroxide free

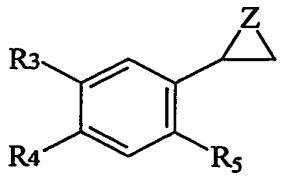
radical of which nitrogen atom is part of a 5-, 6- or 7-membered ring substituted with alkyl groups at positions alpha to the nitrogen;

R^5 is a non-interfering group;

whereas said RO scavenger moieties are optionally substituted with one or more C_1-C_{15} alkyl groups, C_1-C_{15} alkoxy groups, phenyl, —OH, —CH_2OH, and groups capable of donating NO in a charged or neutral form;

and whereas any of said alkyl groups is optionally substituted with one or more functional groups selected from hydroxyl, mercapto, aryl, alkenyl, nitro, and alkoxyl;

which process comprises reacting a chiral or non-chiral epoxide or thioepoxide of the formula



with an amine of the formula H_2N—R^2

wherein Z is oxygen or sulfur;

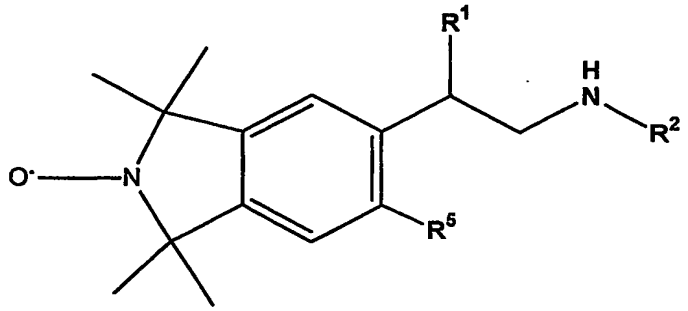
R^2 is a C_5-C_8 cyclic alkyl, or straight or branched C_1-C_{15} alkyl linked to a group selected from a nitroxide free radical, alkenyl, sulfhydryl or dithiol moiety in oxidized or reduced form, aryl, —ONO, —ONO_2, and —SNO; wherein said alkyl is optionally substituted with one or more functional groups selected from hydroxyl, mercapto, aryl, alkenyl, nitro, alkoxyl, C_1-C_5 alkyl, C_1-C_5 alkoxy, phenyl, and —CH_2OH;

and R^3 and R^4 are independently selected from the group consisting of —OH, —CH_2OH, —NHCHO, or R^3 and R^4 together form a nitroxide free radical of which nitrogen atom is part of a 5-, 6- or 7-membered ring substituted with alkyl groups at positions alpha to the nitrogen;

and R^5 is a non-interfering group.

11. A process according to claim 10, wherein said epoxide is prepared from diprotected salicylic acid or salicyl alcohol.

12. A process of preparing a compound of the formula:



or its salt, wherein R^1 is selected from the group consisting of —OH, —ONO, —ONO_2, and —SNO;

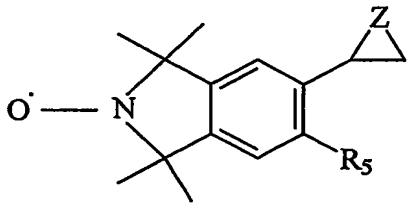
R^2 is ROS scavenger group or a NO donor group connected to the —NH group via a linker made of C_5-C_8 cyclic alkyl, or straight or branched C_1-C_{15} alkyl, wherein said ROS scavenger group is selected from a nitroxide free radical, alkenyl, sulfhydryl or dithiol moiety in oxidized or reduced form, and aryl, and wherein said NO donor group is selected from —ONO, —ONO_2, and —SNO or R^2 is C_5-C_8 cyclic alkyl, or straight or branched C_1-C_{15} alkyl;

and R^5 is a non-interfering group;

whereas said RO scavenger moieties are optionally substituted with one or more C_1-C_{15} alkyl groups, C_1-C_{15} alkoxy groups, phenyl, —OH, —CH_2OH, and groups capable of donating NO in a charged or neutral form;

and whereas any of said alkyl groups is optionally substituted with one or more functional groups selected from hydroxyl, mercapto, aryl, alkenyl, nitro, and alkoxyl;

which process comprises reacting a chiral or non-chiral epoxide or thioepoxide of the formula



with an amine of the formula $H_2N—R^2$

wherein Z is oxygen or sulfur;

R^2 is a C_5-C_8 cyclic alkyl, or straight or branched C_1-C_{15} alkyl linked to a group selected from a nitroxide free radical, alkenyl, sulfhydryl or dithiol moiety in oxidized or reduced form, aryl, —ONO, —ONO_2, and —SNO; wherein said alkyl is optionally substituted with one or more functional groups selected from hydroxyl, mercapto, aryl, alkenyl, nitro, alkoxyl, C_1-C_5 alkyl, C_1-C_5 alkoxy, phenyl, and —CH_2OH;

and R^5 is a non-interfering group.

13. A process according to claim 12, wherein said epoxide is prepared from N-benzylphthalimide.

14. A process according to claims 10 or 12, further comprising converting —SH groups to —SNO groups in the presence of HCl and $NaNO_2$.

15. A multifunctional β-agonist compound of any one of claims 1 to 9 for use as a medicament.

16. A method of treating a respiratory disorder in a mammal in need thereof comprising administering to said mammal an effective amount of a multifunctional β-agonist compound of any one of claims 1 to 9.

17. A method according to claim 16, wherein said disorder is selected from asthma, chronic bronchitis, bronchictiasis and emphysema, chronic obstructive pulmonary disease, chronic obstructive airway disease, and restrictive diseases of the lungs.

18. A method according to claim 16, comprising symptoms selected from recurrent obstruction to air flow within the lung, increased resistance to air flow, narrowing or restriction of an airway, inflammation, bronchial hyperreactivity, airway hyperresponsiveness, mucosal edema, mucus plugging and hypersecretion, and reduced expansion of respiratory parenchyma.

19. A method according to claim 17, wherein asthma is extrinsic or intrinsic.

20. A method according to claim 17, wherein asthma is atopic.

21. A method according to claim 16, wherein said multifunctional β-agonist compound is used in the treatment or prophylaxis of respiratory conditions selected from chronic obstructive pulmonary or airways disease, chronic bronchitis, emphysema, acute respiratory distress syndrome (ARDS) or severe acute respiratory syndrome (SARS) in child or adult, pneumonia, pneumonitis, bronchial hyperreactivity, bronchiectasis, and airway hyperresponsiveness.

22. A method of any one of claims 16 to 21, wherein said administration or treatment is systemic.

23. A method of any one of claims 16 to 21, wherein said administration or treatment is topical

24. A method of claim 16, wherein said β-agonist compound is administered by a route selected from oral, parenteral, intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, implant, buccal, inhalation spray, nasal, vaginal, rectal, and sublingual.

25. A method of claim 16, wherein said mammal is human.

26. A pharmaceutical composition comprising a β-agonist compound of any one of claims 1 to 9.

27. A pharmaceutical composition according to claim 26 comprising salts, solvates, or optical isomers of said compound.

28. A pharmaceutical composition according to claim 26, further comprising carriers, adjuvants, and excipients.

29. A pharmaceutical composition according to any one of claims 26 to 28, further comprising an active agent selected from mucolytic, bronchodilator, muscle relaxant, decongestant, respiratory stimulant, vasodilator, β-agonist, antiallergic, antiasthmatics, analgesic, anti-inflammatory, antibiotic, antifungal, antiprotozoal and antiviral agent.

30. A pharmaceutical composition according to any one of claims 26 to 29, for use as a medicament in treating a disorder selected from asthma, chronic bronchitis, bronchiectasis, emphysema, chronic obstructive pulmonary or airways disease, acute respiratory distress syndrome (ARDS) or severe acute respiratory

syndrome (SARS) in child or adult, pneumonia, pneumonitis, bronchial hyperreactivity, and airway hyperresponsiveness

31. Use of a β-agonist compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, solvate thereof, or an optical isomer thereof, in the preparation of a medicament for treating or preventing a respiratory disorder, substantially as described in the specification.

32. Use according to claim 31, wherein said disorders is selected from the group comprising asthma, chronic bronchitis, bronchiectasis, emphysema, chronic obstructive pulmonary or airways disease, acute respiratory distress syndrome (ARDS) or severe acute respiratory syndrome (SARS) in child or adult, pneumonia, pneumonitis, bronchial hyperreactivity, and airway hyperresponsiveness

33. Use according to claim 31, wherein said disorder comprises symptoms selected from recurrent obstruction to air flow within the lung, increased resistance to air flow, narrowing or restriction of an airway, inflammation, bronchial hyperreactivity, airway hyperresponsiveness, mucosal edema, mucus plugging and hypersecretion, and reduced expansion of respiratory parenchyma.

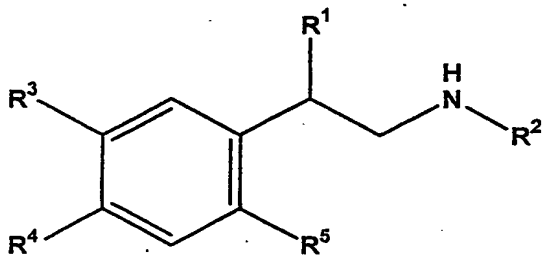
34. A β-agonist compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, for use as a medicament for treating or preventing a respiratory disorder.

35. A method of claim 24, wherein said administration or treatment is via an inhalation device.

36. The method of claim 35 wherein said inhalation device for administering the multifunctional β-agonist compounds, comprises an element selected from

metered dose inhaler, liquid nebulizer, dry powder inhaler, sprayer, and thermal vaporizer.

37. An inhalation device for administering a multifunctional β-agonist compound being ROS scavenger and NO donor of Formula 1:



or its salt, wherein R^1 is selected from the group consisting of —OH, —ONO, —ONO_2, and —SNO;

R^2 is ROS scavenger group or a NO donor group connected to the —NH group via a linker made of C_5-C_8 cyclic alkyl, or straight or branched C_1-C_{15} alkyl in which one carbon atom is optionally replaced by oxygen or nitrogen, wherein said ROS scavenger group is selected from a nitroxide free radical, alkenyl, sulfhydryl or dithiol moiety in oxidized or reduced form, and aryl, and wherein said NO donor group is selected from —ONO, —ONO_2, and —SNO, or R^2 is C_5-C_8 cyclic alkyl, or straight or branched C_1-C_{15} alkyl;

R^3 and R^4 are independently selected from the group consisting of —OH, —CH_2OH, —NH_2, —NHCHO, or R^3 and R^4 together form a substituted 5 to 7-membered saturated heterocycle having 1 or 2 heteroatoms independently selected from nitrogen, and oxygen, and sulfur, or R^3 and R^4 together form amino or hydroxy protecting groups selected from N-formyl, acetal, and ketal;

R^5 is selected from the group consisting of —H, —OH, —CH_2OH, —NH_2, —NHCHO, straight or branched chain C_1-C_{15} alkyl, and straight or branched chain C_1-C_{15} alkoxy;

whereas said RO scavenger moieties are optionally substituted with one or more C_1-C_{15} alkyl groups, C_1-C_{15} alkoxy groups, phenyl, —NH_2, —NHCHO, —OH, —CH_2OH, and groups capable of donating NO in a charged or neutral form; and

whereas any of said alkyl groups is optionally substituted with one or more functional groups selected from hydroxyl, bromo, fluoro, chloro, iodo, mercapto or thio, cyano, alkylthio, aryl, carboxyl, carbalkoyl, alkenyl, nitro, amino, alkoxyl, amido;

wherein at least one of R^1, R^2, R^3 and R^4 comprises at least one ROS scavenger selected from the group of moieties consisting of a nitroxide free radical, alkenyl, sulfhydryl or dithiol in oxidized or reduced form, and aryl; and

wherein at least one of R^1, R^2, R^3 and R^4 comprises at least one NO donor selected from —ONO, —ONO_2, and —SNO;

which device comprises an element selected from metered dose inhaler, liquid nebulizer, dry powder inhaler, sprayer, and thermal vaporizer.

38. A kit comprising an inhalation device, a multifunctional β-agonist of claim 1 in the form of fine power or solution or suspension, wherein said powder or solution or suspension optionally contains other components selected from bulking agent, buffer, carrier, excipient, additive, antioxidant, stabilizer, surfactant, odorant, and a second pharmaceutically active agent.